Table 2. Effect of concentration and solvent composition on the outcome of the IBX · MPO-mediated dehydrogenation reaction.[a]

Entry	Substrate (M)	Solvent	IBX · MPO [equiv]	Time [h]	Yield [%][b]
1	**35** (0.20)	DMSO	1.5	15	0
2	**35** (0.20)	DMSO/THF (1:1)	1.5	15	< 40
3	**35** (0.20)	DMSO/CH_2Cl_2 (2:1)	1.5	6	92
4	**35** (0.20)	DMSO/CH_2Cl_2 (1:1)	1.5	15	91
5	**14** (0.40)	DMSO	2.0	40	68
6	**14** (0.50)	DMSO	2.0	40	72
7	**14** (0.75)	DMSO	2.0	40	87
8	**16** (0.36)	DMSO	2.2	22	82
9	**16** (0.48)	DMSO	2.2	22	76
10	**16** (0.55)	DMSO	2.2	22	73
11	**16** (0.55)	DMSO/CH_2Cl_2 (2:1)	2.2	22	86

[a] Reactions were carried out on a 1.0 mmol scale. [b] Yield of isolated chromatographically pure compound.

dehydrogenation reaction is the subject of continuing research. Elucidation of these features should facilitate further rational designs toward expanding this new area of chemistry whose applications in organic synthesis are expected to be widespread. These results introduce a new paradigm for modifying the iodine(V) nucleus and, hence, controlling its reactivity profile.

Experimental Section

IBX (1.2 mmol) and MPO[12] (1.2 mmol) were added to DMSO (see Table 2 for concentration effect) and stirred at ambient temperature until complete dissolution (15–60 min). The carbonyl compound (0.5 mmol) was added, and the mixture was stirred vigorously at the same temperature. The reaction progress was monitored by thin-layer chromatography. The reaction mixture was diluted with an equal volume of aqueous $NaHCO_3$ (5%) solution and extracted with diethyl ether (3 ×). The combined organic phase was filtered through a pad of celite and then washed with saturated $NaHCO_3$ solution, water, and brine. After drying ($MgSO_4$), the organic layer was concentrated to yield the crude product, which could be further purified by column chromatography (silica gel).

For optimal results in this reaction the following points should be noted: a) in cases in which the substrate was not soluble in the DMSO solution of IBX · MPO, increasing amounts of CH_2Cl_2[13] were added as co-solvent until dissolution, and/or the rate was optimized (see Table 2); b) a large excess of IBX · MPO complex is not recommended, as the rather insoluble IBA formed under these conditions causes precipitation of IBX; in this respect it is also important that the IBX quality is assured by preparation in strict accordance to the method of Santagostino[14] and subsequent checking by means of ^{1}H NMR spectroscopy; c) commercial DMSO (Aldrich) was used directly without prior drying; furthermore, it was noted that anhydrous solvent (sequential drying over activated 4-Å molecular sieves) was deleterious to the yield; d) IBX is light-sensitive, thus the reaction vessel was covered with aluminum foil.[15]

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[9] a) S. D. Meyer, S. L. Schreiber, *J. Org. Chem.* **1994**, *59*, 7549; b) S. De Munari, M. Frigerio, M. Santagostino, *J. Org. Chem.* **1996**, *61*, 9272.
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[11] In addition to the ligands shown in Figure 1, nBu$_3$P=O, tBuOH, 2-picoline-*N*-oxide, and 4-phenylpyridine-*N*-oxide were examined, but the rate of reaction for these complexes was lower than that of uncomplexed IBX under the same conditions.
[12] The commercially available hydrate of MPO, which is considerably less hygroscopic than NMO, was used. The IBX · NMO complex is prepared in the same manner and can also be successfully employed at ambient temperature, although the reaction times are longer and the yields show greater variation with this reagent.
[13] When CH_2Cl_2 is used as cosolvent the reaction rate is retarded; however, its addition was frequently necessary to obtain complete solubility of the substrate (see Table 2, entries 1–4).
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Oxidation of Silyl Enol Ethers by Using IBX and IBX · *N*-Oxide Complexes: A Mild and Selective Reaction for the Synthesis of Enones**

K. C. Nicolaou,* David L. F. Gray, Tamsyn Montagnon, and Scott T. Harrison

Our recent explorations into the chemistry of iodine(V) reagents have highlighted their remarkable synthetic utility.[1–8] In particular, IBX (*o*-iodoxybenzoic acid) has proved to have a rather unique set of properties which can be appropriately exploited to manipulate the course of a reaction.[7, 9] In the preceding paper,[9] we delineated the

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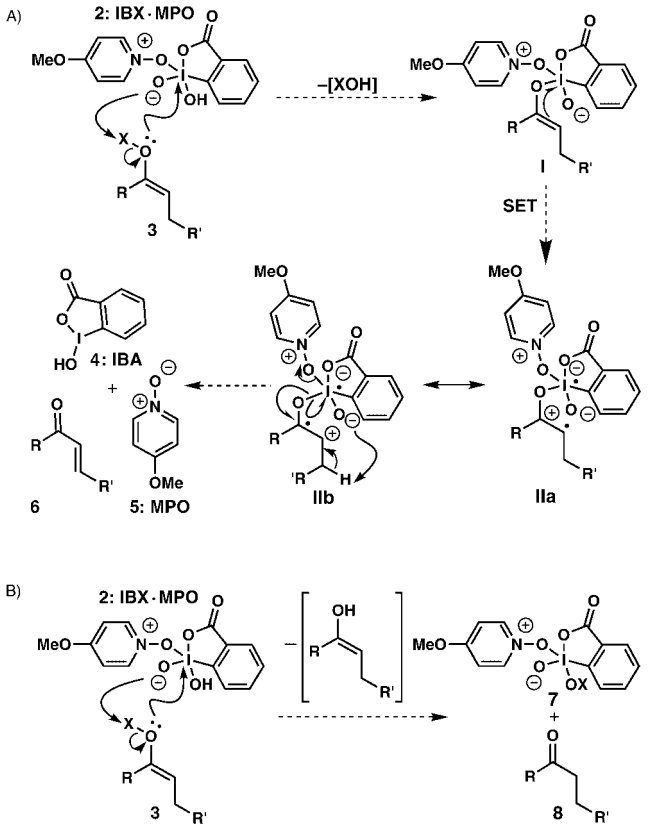
discovery and evolution of IBX · N-oxide complexes and their use in the dehydrogenation of ketones and aldehydes at ambient temperature.[9] We have postulated that these IBX-mediated dehydrogenation reactions[4,7,9] proceed through enolization (facilitated by the reagent) with concomitant capture of the enolate moiety, followed by single electron transfer (SET) to IBX and rearrangement of the resulting radical cation to give the α,β-unsaturated carbonyl compound.[7] This assessment led us to speculate that silyl enol ethers might undergo a similar oxidation with IBX, which would be a new, complimentary oxidation method for the synthesis of the much coveted enone functionality (Scheme 1 A). Herein we report the successful implementation



Scheme 1. Proposed mechanism for A) dehydrogenation, or B) ketone formation, from enol ethers with the IBX · MPO complex.

of this strategy in the conversion of a diverse set of ketones into their α,β-unsaturated counterparts by the fast oxidation of the corresponding TMS enol ethers (for abbreviations, see legends in schemes) induced by IBX (**1**) or the IBX · MPO complex (**2**, Figure 1).[9] We also describe the extension of this powerful method to cascade sequences that involve tandem conjugate additions of organometallic reagents to enones, trapping of the resultant enolates, and regeneration of the original enone motif, thereby increasing the molecular complexity without sacrificing functionality.

The oxidation of silyl enol ethers to enones has frequently been used in the construction of complex molecules, and the multiplicity of protocols available attests not only to its versatility but also to deficiencies in the known methodology

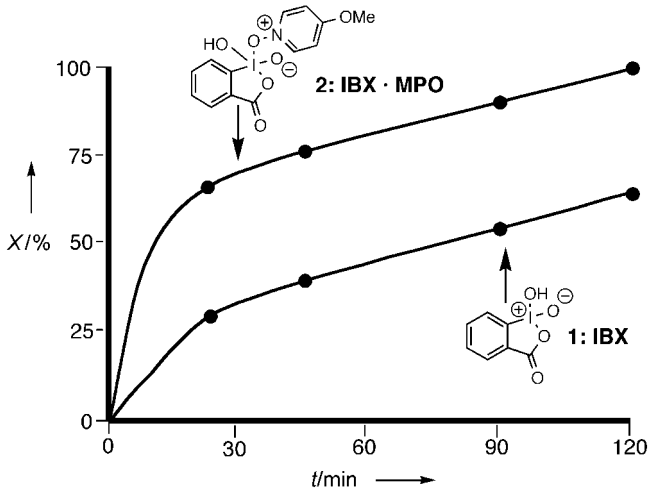


Figure 1. Graph of the rate of conversion of the TMS enol ether derived from cyclooctanone (**31**), to cyclooctenone (**32**) by using IBX (**1**) or IBX · MPO complex (**2**).[29] X = Conversion of TMS enol ether into cyclooctenone (**32**).

for its implementation.[10–16] Amongst the known procedures for this transformation, the palladium-catalyzed protocol,[15, 16] originally introduced by Saegusa and co-workers,[15] stands out by virtue of its relative efficiency and mild nature. However, even within this preferred method, a great variation is seen in the reaction conditions, in the catalyst employed and, ultimately, in the yields of product. These disadvantages, when added to the expense associated with the use of palladium and its incompatibility with various functional groups, allow considerable room for improvement in this area. As our investigations with hypervalent iodine(v) reagents evolved, it was gratifying to discover the remarkable ease with which IBX-based reagents, particularly the IBX · MPO complex (**2**, Figure 1), converted TMS enol ethers into α,β-unsaturated carbonyl compounds.

As shown in Table 1, a wide variety of sensitive functionalities can be tolerated under the employed conditions; the reaction times are short, and the yields are often very high. Thus, substrates that contain reactive functionalities, for example, amines, sulfides, mesylates, TBS ethers, dithianes, or primary iodides (Table 1, entries 2, 3, 6, 9, 12, and 13) all furnished the desired enones in high yield. Significantly, the protocol works well in a number of situations which caused problems with known methods. For example, generation of allylic epoxide **30** proceeds in high yield (Table 1, entry 10) and a proximal, but unconjugated olefin in the product **26** (Table 1, entry 8) remains unaffected under these conditions. Furthermore, a survey of the literature[17–19] revealed that the oxidation of indanones to form indenones is frequently cumbersome or can be plagued by low yields or multiple by-products. In contrast, the current method performs admirably well in this challenging situation (Table 1, entries 4 and 5), and furnishes the corresponding enones in yields that significantly exceed those obtained by the best published procedure ($<75\,\%$), which involves the use of a stoichiometric amount of $Pd(OAc)_2$ to oxidize the silyl enol ether.[19] Although the oxidation of cyclooctanone (**31**; Table 1, entry 11) may appear trivial, this specific ring size, and hence strain, leads to a lack

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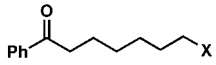
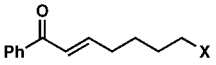
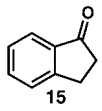
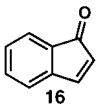
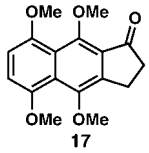
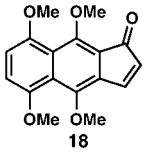
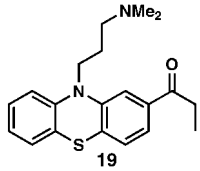
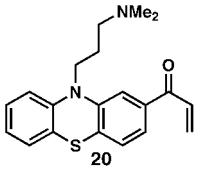
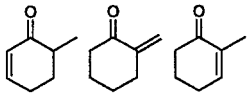
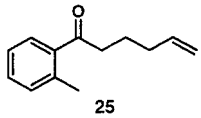
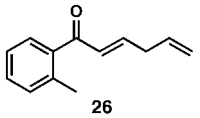
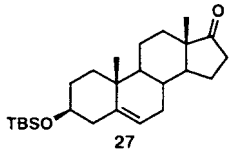
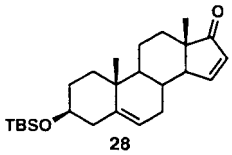
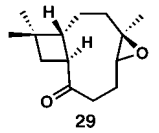
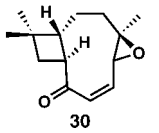
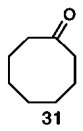
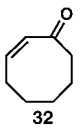
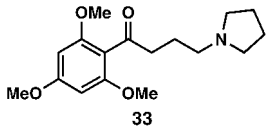
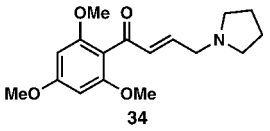
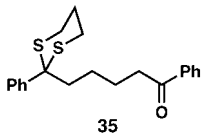
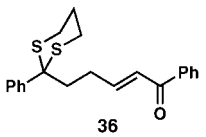
Table 1. Facile room temperature dehydrogenation of ketones via the corresponding trimethylsilyl enol ethers by using IBX · MPO complex.[a]

Entry	Substrate	Product	TMS enol ether formation[b]	IBX · MPO [equiv]	Time [min]	Yield [%][c]
			A	1.5	40	96
1	**9: X = OMe**	**10: X = OMe**				
2	**11: X = OSO_2Me**	**12: X = OSO_2Me**	A	1.5	40	92
3	**13: X = I**	**14: X = I**	A	1.5	40	88
4	 **15**	 **16**	A	1.3	40	94
5	 **17**	 **18**	A	1.5	30	95
6	 **19**	 **20**	C	3.0	240	72[d]
7	 **21**	 1 : 5 : 3 **22** **23** **24**	B	1.5	60	94[e]
8	 **25**	 **26**	A	1.5	40	94
9	 **27**	 **28**	C	1.5	60	62[f]
10	 **29**	 **30**	C	1.5	40	93
11	 **31**	 **32**	A	1.1	20	96
12	 **33**	 **34**	C	4.0	360	43[g]
13	 **35**	 **36**	C	2.0	120	76

[a] Reactions were carried out on a 0.1 – 5.0 mmol scale in DMSO/CH_2Cl_2 (see main text for discussion). [b] A: ref. [20], B: ref. [21], C: ref. [22]. [c] Yield of isolated chromatographically pure compound, except where stated. The starting ketone was frequently recovered as the product of enol ether hydrolysis but is only noted when > 10 %. [d] Plus 23 % inseparable ketone, ratio assigned by means of ^{1}H NMR spectroscopy. [e] Product distribution assigned by means of ^{1}H NMR spectroscopy. [f] Plus 33 % ketone. [g] Plus 52 % inseparable ketone, ratio assigned by means of ^{1}H NMR spectroscopy. MPO = 4-methoxypyridine-*N*-oxide.

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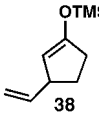
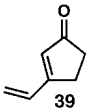
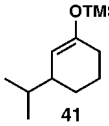
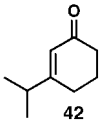
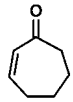
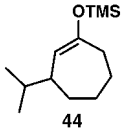
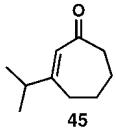
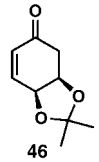
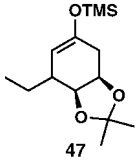
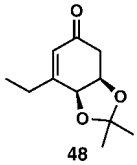
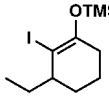
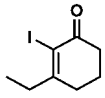
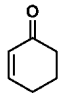
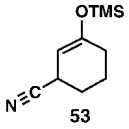
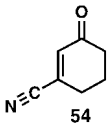
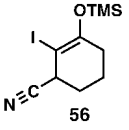
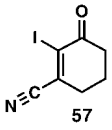
of specificity in the alternate IBX methodologies,[7, 9] in which the dienone is a major component of the product mixture. However, the present method allows for the introduction of just one double bond through the formation of the silyl enol ether, followed by oxidation with **2**.

The method is not without limitations, as substituents at the α position of the ketone substrate lead to some complications, including the regioselective generation of the silyl enol ether, an issue which is amply covered in the literature.[20–22] In the simplest case of α substitution that we examined (Table 1, entry 7) the oxidation reaction is essentially nonselective (*exo*/*endo* ca. 5:3). With compounds that bear a phenyl group at the α position, the desired oxidation reaction was unfeasible as a result of the propensity of the highly stabilized incipient radical cation (e.g. **II a**, Scheme 1 A) to dimerize. The influence of steric hindrance around the carbonyl group could not be easily evaluated owing to the difficulties in accessing a range of α-substituted substrates (see above). However, an adjacent tertiary center (Table 1, entry 9) and an iodine atom (Table 2, entries 5 and 7) are both well tolerated. In a number of examples (e.g. Table 1, entries 6, 9, and 12), the alternate reaction pathway, that is, hydrolysis of the silyl enol ether back to the original starting ketone (Scheme 1 B), proved to be of greater significance. There are generally two reasons for this observed side reaction. First, the insolubility of the substrate in DMSO, such as with a steroid-derived enol ether (Table 1, entry 9), which required the addition of a large volume of CH_2Cl_2, thus leading to a slower oxidation reaction and competing hydrolysis.[23] In the enol ethers derived from substrates **19**, **33**, and **35** (Table 1, entries 6, 12, and 13) coordination to the oxidant through heteroatoms may be responsible for the need to use excess IBX, thus leading to the retardation of the desired reaction and varying degrees of competing hydrolysis. The second reason relates to the reactivity of the silyl enol ether (Table 2, entry 1). Thus, when highly reactive species were utilized, hydrolysis was rapid (even beginning upon isolation of the enol ether), and oxidation was compromised. This result precluded the inclusion of silyl ketene acetals as substrates for this method.

Incorporation of the current oxidation method within a cascade reaction could allow a rapid increase in molecular complexity. Particularly attractive appeared to be a sequence that involved conjugate addition to an enone, followed by in situ silyl enol ether formation, and subsequent isolation and oxidation of the resulting product to regenerate a new enone functionality for further elaboration. Table 2 summarizes the results of the implementation of this strategy. Thus, the addition of cuprate reagents (RMgX, $CuBr \cdot SMe_2$) to enones **37**, **40**, **43**, and **46** (Table 2, entries 1–4) followed by quenching with TMSCl and oxidation of the resulting silyl enol ethers with IBX (**1**) or IBX·MPO (**2**) furnished the elaborated enones **39**, **42**, **45**, and **48**, respectively, in high overall yields. Some of these products were difficult to synthesize by means of alternative protocols.[24] This is particularly true for the sensitive enone product **48**, which was difficult to obtain from the corresponding saturated ketone. This protocol was extended to the synthesis of enones substituted at the α-position with iodine (Table 2, entries 5 and 7) and at the β position with cyanide (Table 2, entries 6 and 7) by the use of Et_2AlCN.[25]

Table 2. Dehydrogenation of trimethylsilyl enol ethers, formed in situ from an enone.[a]

Entry	Substrate	Silyl enol ether	Product	Yield [%][b]
1	 **37**	 **38**	 **39**	90[c]
2	 **40**	 **41**	 **42**	97[d]
3	 **43**	 **44**	 **45**	94
4	 **46**	 **47**	 **48**	47[c,d]
5	 **49**	 **50**	 **51**	98
6	 **52**	 **53**	 **54**	98
7	 **55**	 **56**	 **57**	82[c]

[a] Reactions were carried out on a 2.0 mmol scale. [b] Overall yield of pure isolated compound, no chromatography required. [c] Chromatography required to separate enone from hydrolysis product. [d] Oxidation performed without complex, IBX (1.5–2.0 equiv) added as a solid to a solution of enol ether in DMSO (see 2 below). Reagents and conditions: Entries 1–5; 1) $CuBr \cdot SMe_2$ (2.0 equiv), THF, $-78\,^{\circ}C$ add RMgX (4.0 equiv), 30 min; then add TMEDA (4.0 equiv), TMSCl (5.0 equiv), enone (1.0 equiv) in THF, $-78 \rightarrow 25\,^{\circ}C$, 30 min. Entries 6 and 7; 1) Et_2AlCN (1.3 equiv), hexanes, $-10\,^{\circ}C$, add enone, 90 min; then pyridine (4.0 equiv), TMSCl (3.7 equiv), $-10 \rightarrow 25\,^{\circ}C$, 2 h. 2) Add preformed solution of IBX·MPO complex (1.5–2.0 equiv, 0.4 M in DMSO) to substrate, vigorous stirring, 30– 60 min. TMS = trimethylsilyl. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

IBX (**1**) and IBX·MPO complex (**2**) were examined in their reactions with a range of enol ethers derived from cyclohexanone (Table 3). Only the TBS enol ether **58 c** was inert to the reaction conditions, as all the remaining substrates led to ketone **59** and/or enone **60** as products. The extent to which the enone arose from the complex-mediated dehydrogenation of the corresponding saturated ketone[9] was not significant, although it was found to be dependent on the substrate. The oxidation of the TES enol ether **58 b** was, as predicted, slower than that of the TMS enol ether **58 a**. When the TES enol ether was used in more sophisticated examples

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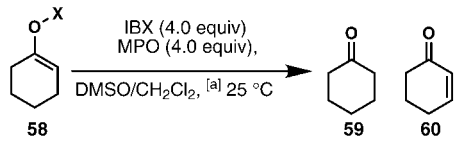
Table 3. Reactions of various enol ether derivatives of cyclohexanone with IBX · MPO complex.



Enol ether		Products[b]					Time [h]
58	X	**58**		**59**		**60**	
a:	TMS	0	:	0	:	1	1
b:	TES	0	:	1	:	18	8
c:	TBS	1	:	0	:	0	12
d:	Ac	8	:	1	:	0	12
e:	Me	3	:	6	:	1	2
f:	$CH_2CH{=}CH_2$	3	:	8	:	1	1

[a] see main text for discussion. [b] Ratios determined by ^{1}H NMR spectroscopy.

such as steroid **27** and amine **33** (Table 1, entries 9 and 12), no significant dehydrogenation occurred, with hydrolysis being the major pathway. The ease with which IBX effects hydrolysis of the relatively stubborn **58e** may be readily rationalized by the mechanism shown in Scheme 1B, since both the Lewis acidity and nucleophilicity of IBX are well known.[26] We propose that the oxidation reaction of TMS enol ethers is likely to proceed through a SET pathway by analogy to the original IBX-based method (Scheme 1A).[7]

In conclusion, we have developed an extremely mild and efficient procedure for the oxidation of silyl enol ethers to the corresponding α,β-unsaturated carbonyl compounds through the use of IBX (**1**) or its MPO complex **2**, which is complimentary to the method delineated in the preceding paper.[9] By careful selection of one of these two protocols, based on the substrate features, a diverse set of carbonyl compounds can now be dehydrogenated with ease. This method exhibits a broad scope, affords clean products in high yields, and is expected to find wide-ranging applications in organic synthesis.

Experimental Section

Typical procedure: IBX[27] and MPO[28] (1.1 to 4.0 equiv) were dissolved in DMSO (0.4 M) in an equimolar ratio at ambient temperature. The solvent used was not dried, and no precautions were taken to exclude moisture or oxygen from the reaction vessel. The TMS enol ether was generated by using one of a number of established procedures (depending on the substrate) from the carbonyl compound (1.0 equiv).[20–22] The crude TMS enol ether was vacuum-dried wherever possible to minimize the amount of $(TMS)_2O$ present, as this was detrimental to the desired reaction. The IBX · MPO solution was added in one portion at ambient temperature to the crude TMS enol ether dissolved in a minimum of DMSO. In cases in which the substrate was not completely soluble in DMSO, CH_2Cl_2 was added dropwise to the suspension (or emulsion) until clear. The CH_2Cl_2 content was always minimized, as its use as a cosolvent retards the reaction.[4, 23] The solution was stirred vigorously, and progress was monitored by means of thin-layer chromatography. Upon completion, the reaction mixture was diluted with aqueous $NaHCO_3$ (5%) and extracted with diethyl ether (3 ×). The combined organic phase was filtered through a pad of celite and washed with saturated aqueous $NaHCO_3$, water, and brine. After drying ($MgSO_4$), the solvent was removed in vacuo to yield the crude product, which could be purified further by means of column chromatography.

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[20] Procedure A involved the generation of the silyl enol ether at 0 °C in CH_2Cl_2 (0.2 M solution) by treatment with Et_3N (3.0 – 9.0 equiv) followed by addition of TMSOTf (1.5 – 3.0 equiv); the workup was the same as that described in ref. [21b]; OTf = trifluoromethanesulfonate.

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[22] Procedure C involved the generation of the silyl enol ether by deprotonation of the ketone at −40 °C in THF (NaHMDS, 1.0 M solution in THF, 1.2 equiv) followed by quenching with TMSCl (1.5 equiv) at −40 °C and subsequent warming to 0 °C; the workup was the same as that described in ref. [21b]; HMDS = hexamethyldisilazane.

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[27] Complex **2** was found to be the fastest agent for effecting this oxidation, as was the case for the ambient temperature dehydrogenation of carbonyl compounds,[9] although IBX (**1**) itself could be used without any detriment to the reaction in simpler cases.

[28] The commercially available hydrate of MPO was used.

[29] In this case, the reaction was carried out at higher dilution to give a timescale appropriate for accurate monitoring by means of ^{1}H NMR spectroscopy.

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